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Catalytic Trifluoromethylation of Aryl- and Vinylboronic Acids by 2-Cyclopropyl-1-(trifluoromethyl)benzo[*b*]thiophenium Triflate

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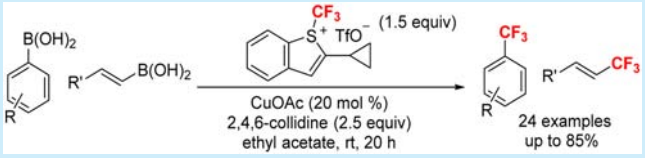
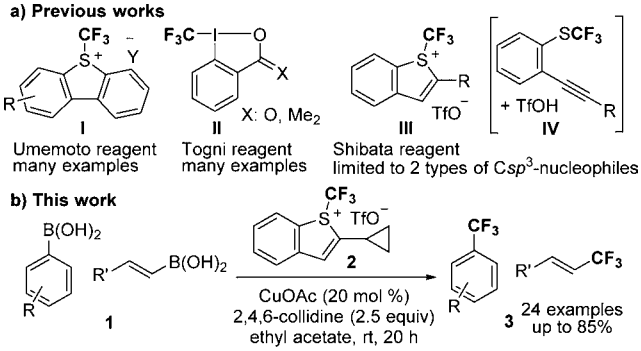
Supporting Information

ABSTRACT: Catalytic trifluoromethylation of aryl- and vinylboronic acids by 2-cyclopropyl-1-(trifluoromethyl)benzo-[*b*]thiophenium triflate is described. In the presence of a catalytic amount of CuOAc and 2,4,6-collidine in ethyl acetate, the reaction proceeded in good to high yields for various substrates under mild reaction conditions at room temperature.



Organofluorine compounds have been increasingly recognized as crucial contributors in specialty materials and the pharmaceutical and agrochemical industries over the past decade.[1] In particular, trifluoromethylated aromatic (CF_3Ar) compounds are widely used in a key component of drugs on the market such as cinacalcet and fipronil.[1e,2] More recently, they have been sought after as key functional units of asymmetric catalysts and ligands for organic reactions.[3] Since simple CF_3Ar derivatives are popular as raw materials, an efficient and scaleable synthesis of CF_3Ar compounds using inexpensive reagents is required.[4] On the other hand, direct introduction of a CF_3 group into aromatic compounds is suitable in a late stage of the synthetic sequence.[5,12] Late-stage direct trifluoromethylation using a shelf-stable trifluoromethylation reagent appears to be highly advantageous for drug discovery strategies by allowing novel pharmacophores to be devised, synthesized, and screened. In this context, shelf-stable electrophilic trifluoromethylation reagents have been the focus of attention, and several types of reagents have been reported, including reagents by Yagupol'skii,[6] Umemoto,[7] Shreeve,[8] and Togni.[9] We also reported original reagents, (trifluoromethyl)-sulfoximinium and 5-thiophenium salts.[10,11] The amount of literature published using Umemoto reagent **I** and Togni reagent **II** has been rapidly growing in recent years, and a variety of trifluoromethylation reactions have been possible by many researchers using these reagents.[12,14] On the other hand, the utility of our reagent **III** has been somewhat limited to the electrophilic trifluoromethylation of Csp^3-carbon nucleophiles such as *β*-keto esters and dicyanoalkylidenes,[11] and they are not effective for trifluoromethylation of Csp^2-carbon such as aromatic compounds and vinylic compounds, due to the instability under the coupling conditions.[13] In 2013, Médebielle and co-workers carefully investigated the electrochemical behavior of Umemoto reagent **I**, Togni reagent **II**, and our sulfonium-based reagents, including **III**, in anhydrous acetonitrile, *N*,*N*-dimethylformamide (DMF), and methanol using cyclic voltammetry.[13] That study found that Umemoto reagent **I** and our reagent **III** were superior electron acceptors and were likely to be better sources of trifluoromethyl radical(s) generated upon electrochemical reduction. However, in contrast to Umemoto reagent **I** and Togni reagent **II**, our reagent **III** is unstable in DMF, inducing ring-opening of **III** to **IV** (Scheme 1a). This could be one of the reasons for the limitation of **III**[11] despite its superior electron-acceptor property.[13]

Scheme 1. (a) Electrophilic Reagents I–III. (b) Copper-Catalyzed Trifluoromethylation of Boronic Acids with 2



Toward expanding the utility of **III**, we envisaged that this problem could be simply overcome by selecting a suitable solvent for target transformations. We disclose herein the copper-catalyzed trifluoromethylation of aryl- and vinylboronic acids **1** using our reagent **III**, 2-cyclopropyl-1-(trifluoromethyl)-benzo[*b*]thiophenium triflate (**2**). As expected, the choice of solvent was found to be key to the success of the reaction, and conditions consisting of a catalytic amount of CuOAc and 2,4,6-collidine in ethyl acetate were effective for trifluoromethylation of various arylboronic acids **1** to provide corresponding CF_3 compounds **3** in good to high yields under mild reaction conditions. The method was also found to be applicable for trifluoromethylation of vinylboronic acids **1** (Scheme 1b).

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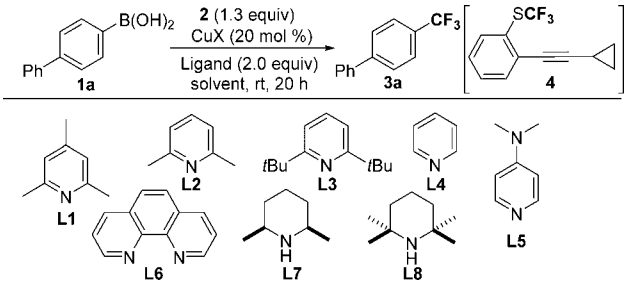
Table 1. Optimization of the Copper-Catalyzed Trifluoromethylation of 4-Biphenylboronic Acid 1a with 2[a]



run	CuX	L	solvent	ε_r[b]	SB	yield[c] (%)
1	CuOAc	**L1**	DMAc	38.8	0.650	43 (54)
2	CuOAc	**L1**	DMF	38.3	0.613	49 (49)
3	CuOAc	**L1**	acetonitrile	36.6	0.286	5 (96)
4	CuOAc	**L1**	THF	7.52	0.591	54 (41)
5	CuOAc	**L1**	diethyl ether	4.27	0.562	27 (56)
9	CuOAc	**L1**	DME	7.30		48 (58)
7	CuOAc	**L1**	1,4-dioxane	2.22	0.444	56 (47)
8	CuOAc	**L1**	CH_2Cl_2	8.99	0.178	43 (59)
9	CuOAc	**L1**	$ClCH_2CH_2Cl$	10.4	0.126	29 (69)
10	CuOAc	**L1**	ethyl acetate	6.08	0.542	74 (32)
11	CuOAc	**L2**				44 (57)
12	CuOAc	**L3**				15 (57)
13	CuOAc	**L4**				4 (79)
14	CuOAc	**L5**				0 (69)
15	CuOAc	**L6**				0 (92)
16	CuOAc	**L7**				37 (11)
17	CuOAc	**L8**				22 (47)
18[d]	CuOAc	**L1**				25 (75)
19[e]	CuOAc	**L1**				45 (38)
20	CuCl	**L1**				55 (38)
21	CuBr	**L1**				36 (52)
22	CuI	**L1**				10 (88)
23	$(Cu(OTf))_2$-toluene	**L1**				39 (90)
24	CuTc[f]	**L1**				69 (16)
25[g]	CuOAc	**L1**				77 (37)
26[g,h]	CuOAc	**L1**				87 (34)

[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.33 mmol), CuX (20 mol %), ligand (0.50 mmol), solvent (1.25 mL), rt, 20 h, under N_2 atmosphere. [b]T = 293.2 K. [c]^{19}F NMR yields of **3a** with PhF (0.75 mmol) as an internal standard and the values in parentheses are ^{19}F NMR yields of **4**. [d]**L1** (0.10 mmol), NaOAc (0.50 mmol) were used. [e]**L1** (0.10 mmol), K_2CO_3 (0.50 mmol) were used. [f]CuTc = Cu-thiophene-2-carboxylate. [g]**2** (0.38 mmol) was used. [h]**L1** (0.63 mmol) was used.

The optimization of the trifluoromethylation conditions was carried out using 4-biphenylboronic acid (**1a**) with **2** as a model reaction (Table 1). We first attempted the trifluoromethylation of **1a** under the best conditions for a similar aromatic trifluoromethylation reaction using Umemoto reagent **I** reported by Liu and co-workers;[14] a catalytic amount of CuOAc (20 mol %) and 2,4,6-collidine **L1** (2.0 equiv) in *N*,*N*-dimethylacetamide (DMAc) at room temperature. The desired CF_3 product **3a** was produced in 43% yield determined by ^{19}F NMR spectroscopy with an internal standard in the reaction condition (run 1), while a substantial amount of ring-opening SCF_3 compound **4** was also detected in 54% yield. Under the same reaction conditions, but in DMF, product **3a** was obtained in 49% yield with 49% of SCF_3 compound **4** (run 2). In acetonitrile, the ring opening of **2** to **4** was a major reaction (96%), and the trifluoromethylation was detected only in 5% (run 3). Further solvent screening served as an additional approach, since we anticipated the dielectric constant of solvent (ε_r)[15] and basicity of the solvent (SB)[16] might affect the reactivity, solubility, and stability of the reagent **2** (runs 1−10). Interestingly, the use of ethyl acetate was most effective for this transformation to yield **3a** in 74% yield, and the ring-opening of **2** to **4** was reduced to 32% (run 10). Ethyl acetate has a medium dielectric constant (6.08), while that of DMAc (38.8) and DMF (38.3) are much higher, and those of diethyl ether (4.27) and 1,4-dioxane (2.22) are lower. The higher dielectric constant of the solvent might break an intimate ion pair of thiophenium and the triflate of **2** by solvation to induce the ring-opening of **2** to **4**. On the other hand, the basicity of solvent (SB) did not seem to be closely related to the reactivity and stability of **2**. Since ethyl acetate was found to be suitable for this reaction, we next screened ligands for this reaction (runs 11−17). The ligand screening revealed that other ligands, **L2**−**L8**, dramatically decreased the formation of **3a**. In particular, the ligands **L4**−**L6** significantly inhibited the formation of **3a**, while the ring-opening of **2** was detected in

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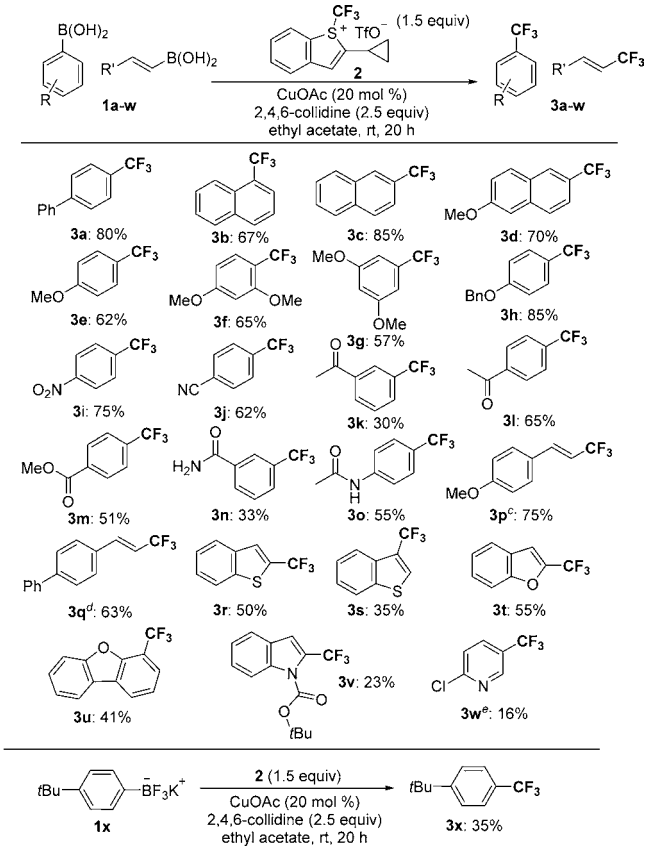
69−92% yield (runs 13−15). These ligands presumably act as a base as well to catalyze the ring-opening reaction of **2** to **4**, while ligands **L1**−**L3**, **L7**, and **L8**, having neighboring alkyl groups on the nitrogen atom, do not behave as a strong base due to steric hindrance. This is supported by the fact that yields decreased to 25−45% after the addition of a base such as NaOAc and K_2CO_3 (runs 18 and 19). We further optimized the copper catalyst. Copper halides such as CuCl, CuBr, and CuI gave lower yields of **3a** (runs 20−22). CuTc gave yields comparable to those with CuOAc. Finally, a slight increase in the amount of **2** and **L1** improved the yield of **3a** to 77−87% (runs 25 and 26).

With the optimized conditions in hand (Table 1, run 26), we explored the scope of the trifluoromethylation reaction with diverse aryl- and vinylboronic acids **1**. The results are summarized in Scheme 2. It was found that various aryl- and vinylboronic acids were trifluoromethylated to the desired products **3** in modest to high yields. Simple phenylboronic acids **1a**−**c** were transformed into the trifluoromethylated products **3a**−**c** in high yields. Arylboronic acids **1d**−**h** bearing an electron-donating group (OMe) reacted smoothly independent of the number of MeO groups as well as its position on the aromatic ring to provide **3d**−**h**. Substrates **1i**−**m** with electron-withdrawing groups (NO_2, CN, carbonyl, and ester) on the benzene ring were also acceptable, and the corresponding trifluoromethylated compounds **3i**−**m** were obtained in good yields. Amide substituents on the aryl moiety **1n**,**o** were also tolerated during the reaction, although the free amide derivative **3n** was obtained in 33% yield. We confirmed that vinylboronic acids **1p**,**q** also were converted effectively into trifluoromethyl vinyl products **3p**,**q** in 63−75% yields. In addition, the heteroaryl substrate, 2- and 3-benzothiopheneboronic acid **1r**,**s**, 2-benzofuranboronic acid **1t**, and dibenzofuranboronic acid **1u** were trifluoromethylated with **2**, with good yields of 35−55% for **3r**−**u**. Moreover, 2-indoleboronic acid **1v** and 5-pyridneboronic acid **1w** were applicable for the trifluoromethylation reaction under the same conditions to provide **3v** and **3w**, respectively. We finally found that trifluoroborate **1x**, instead of boronic acids, was also tolerated in the trifluoromethylation reaction under the same conditions, although the yield of **3x** was rather low of 35%.

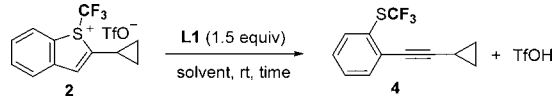
Scheme 2. Scope of the Substrates[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.38 mmol), CuOAc (20 mol %), 2,4,6-collidine (0.63 mmol), ethyl acetate (1.25 mL), rt, 20 h, under nitrogen atmosphere. [b]Isolated yield. [c]E/Z = 33/1. [d]E/Z = 50/1. [e]^{19}F NMR yield with PhF (0.75 mmol) as an internal standard.

In order to understand the solvent effect on this transformation, we further examined the stability of **2** in each solvent (Table S1, Supporting Information). Interestingly, in spite of the moderate yields of **3a** obtained in amide solvents (43% in DMAc and 49% in DMF, runs 1 and 2, Table 1), a prompt ring-opening of **2** to **4** was observed in DMAc (61%) and in DMF (100%) for 1 h (runs 1 and 2, Table S1, Supporting Information).[13] On the other hand, **2** is rather stable in other solvents (runs 3−10, Table S1, Supporting Information), but the yields of **3a** in these solvents were widely varied (runs 3−10, Table 1); for example, in acetonitrile, chlorinated solvents (CH_2Cl_2, $ClCH_2CH_2Cl$) and ethyl acetate (runs 3, 8−10 in Table S1 (Supporting Information) vs runs 3 and 8−10 in Table 1). The stability of **2** was further investigated with selected solvents in the presence of ligand **L1** (Table 2). We confirmed that the ring-opening of **2** to **4** is significantly slower in ethyl acetate (run 4) compared to ring-opening in DMAc, acetonitrile, and CH_2Cl_2 (runs 1−3). The results were closely related to the solubility of **2** in solvents (Table 3). Moreover, the solubility of **2** is highly related to the dielectric constant of

Table 2. Ring-Opening of 2−4 under Basic Conditions[a,b]



		yield of **4**[b] (%)			
run	solvent	1 h	5 h	10 h	20 h
1	DMAc	94	100	100	100
2	acetonitrile	85	100	100	100
3	CH_2Cl_2	68	100	100	100
4	ethyl acetate	6	18	18	19

[a]Reaction conditions: **2** (0.10 mmol), **L1** (0.15 mmol), $PhCF_3$ (0.10 mmol), solvent (0.5 mL), rt, under N_2 atmosphere. [b]^{19}F NMR yields with an internal standard $PhCF_3$.

Table 3. Solubility and Stability of 2[a]

run	solvent	solubility of **2** + **4**[b] (%)	ε_r[c]
1	DMAc	100 (**2**/**4** = 0/100)	38.8
2	acetonitrile	100 (**2**/**4** = 100/0)	36.6
3	CH_2Cl_2	8 (**2**/**4** = 3/1)	8.99
4	ethyl acetate	<3 (**2**/**4** = 100/0)	6.08

[a]Experimental conditions: **2** (0.10 mmol), $PhCF_3$ (0.10 mmol), solvent (0.5 mL), rt, 1 h, under N_2 atmosphere. [b]Analyzed by ^{19}F NMR with $PhCF_3$ as an internal standard. [c]T = 293.2 K.

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solvent (ε_r). These results indicate that the ring-opening of **2** to **4** should be promoted by the ligand as a base, but the poor solubility of **2** in ethyl acetate affected the inhibition of this ring-opening. In addition, the coordination of solvent such as DMF and DMAc to copper is a positive factor to promote the coupling reaction. Based on these results, we concluded that ethyl acetate would have the suitable balance of poor solubility (= good stability) of **2** and coordination ability (= reactivity), although it needs greater discussion.

In summary, we have developed a copper-catalyzed trifluoromethylation reaction of aryl-, heteroaryl-, and vinylboronic acids **1** with 2-cyclopropyl-1-(trifluoromethyl)benzo[*b*]thiophenium triflate (**2**). The reaction proceeds under mild conditions and tolerates various substrates having electron-donating or electron-withdrawing groups and a heteroaryl group. Selection of the solvent such as ethyl acetate allowed the aromatic trifluoromethylation of boronic acids, which was previously problematic, to be realized. Trifluoroborate was also useful as a coupling partner of this transformation. Until now, reagent **2** has not been actively researched due to its instability in some solvents.[11,13] We expect reagent **2** to become more popular for other types of trifluoromethylation reagents after solvent screening.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (e) Jeschke, P. *ChemBioChem* **2004**, *5*, 570.

(2) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Pozo, C. d.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(3) (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137. (b) Zhao, H.; Qin, B.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 6822. (c) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666. (d) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3707.

(4) (a) Pouterman, E.; Girardet, A. *Helv. Chim. Acta* **1947**, *30*, 107. (b) Alexandere, P.; Stephane, C.; Sylvette, B. *J. Fluorine Chem.* **2010**, *131*, 1241.

(5) (a) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, *47*, 4095. (b) Kondratenko, N. V.; Vechirko, E. P.; Yagupolskii, L. M. *Synthesis* **1980**, 932. (c) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832. (d) Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009**, 1909. (e) Morimoto, H.; Tsubogo, T.; Livitinas, N. D.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2011**, *123*, 3877. (f) Tomashenko, O. A.; Escudero-Adán, E. C.; Belmonte, M. M.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2011**, *123*, 7797. (g) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Waston, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679.

(6) Yagupol'skii, L. M.; Kondratenko, N. V.; Timolfeeva, G. N. *J. Org. Chem. USSR* **1984**, *20*, 103.

(7) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579.

(8) Yang, J.-J.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1998**, *63*, 2656.

(9) Eisenberger, P.; Gischig, S.; Togni, A. *Chem, Eur. J.* **2006**, *12*, 2579.

(10) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465.

(11) Matsnev, A.; Noritake, S.; Nomura, Y.; Tokunaga, E.; Nakamura, S.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 572.

(12) (a) Zhang, C. *Org. Biomol. Chem.* **2014**, *12*, 6580. (b) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (c) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. (d) Liu, T.; Shen, Q. *Org. Lett.* **2011**, *13*, 2342. (e) Weng, Z.; Li, H.; He, W.; Yao, L.-F.; Tan, J.; Chen, J.; Yuan, Y.; Huang, K.-W. *Tetrahedron* **2012**, *68*, 2527. (f) Deng, Q.-H.; Wadepohl, H.; Gade, L.-H. *J. Am. Chem. Soc.* **2012**, *134*, 10769. (g) Egami, H.; Shimizu, S.; Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000. (h) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (i) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. (j) Yasu, Y.; Koike, T.; Akita, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567. (k) Dai, J.-J.; Fang, C.; Xiao, B.; Yi, J.; Xu, J.; Liu, Z.-J.; Lu, X.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8436.

(13) Mizuta, S.; Verhoog, S.; Wang, X.; Shibata, N.; Gouverneur, V.; Médebielle, M. *J. Fluorine Chem.* **2013**, *155*, 124.

(14) Xu, J.; Luo, D.-F.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Fu, Y.; Liu, L. *Chem. Commun.* **2011**, *47*, 4300.

(15) Haynes, W. M.; Lide, D. R.; Bruno, T. J. *CRC Handbook of Chemistry and Physics*, 93rd ed.; Taylor & Francis: New York, 2012.

(16) Catalán, J.; Díaz, C.; López, V.; Pérez, P.; Paz, J. -L. G.; Rodríguez, J. G. *Liebigs. Ann. Chem.* **1996**, 1785.

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